Lifetime Marijuana Use and Subclinical Atherosclerosis: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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ABSTRACT

Background and aims: Unlike tobacco, the effect of marijuana smoke on subclinical atherosclerosis, a surrogate measure for cardiovascular disease, is not known. This study aimed to determine the association between lifetime exposure to marijuana and measures of subclinical atherosclerosis in mid-life.

Design, setting and participants: We used data from the US-based Coronary Artery Risk Development in Young Adults (CARDIA) Study, a cohort of black and white men and women aged 18-30 years at baseline in 1985-86, with up to 7 follow-up exams over 25 years. The number of CARDIA participants included in this study was 3,498.

Measurements: Cumulative years of exposure to marijuana (expressed in 'marijuana-years', with 1 marijuana-year equivalent to 365 days of use) using repeated assessments every 2-5 years, over 25 years. Abdominal artery calcium (AAC) and coronary artery calcium (CAC) scores measured by computed tomography at Year 25 exam.

Results: Among 3,117 participants with AAC and CAC measurements, 2,627 (84%) reported past marijuana use and 1,536 (49%) past daily tobacco smoking. Compared with tobacco smokers, of which 46% reported 10 or more pack-years of use, only 12% of marijuana users reported 5 or more marijuana-years of use and only 6% reported having used marijuana daily. We found a significant interaction between never- and ever- tobacco users on the association between cumulative marijuana use and AAC (p=0.05). Among those who never smoked tobacco, cumulative marijuana-years were not associated with AAC or CAC in models adjusted for demographics, cardiovascular risk factors, licit and illicit

drug exposure and depression symptoms. However, among ever tobacco smokers, marijuana exposure was associated with AAC and CAC. At 5 marijuana-years of exposure, using AAC=0 and CAC=0 as a reference group, the odds ratio (OR) was 1.97 (95%CI:1.21-3.21,p=0.007) for AAC>0/CAC=0 and 1.83 (95%CI:1.02-3.31,p=0.04) for CAC>0, regardless of AAC. Tobacco smoking was strongly associated with both AAC and CAC.

Conclusion: Marijuana use appears to be associated with subclinical atherosclerosis, but only among ever tobacco users.

Keywords: Marijuana, tobacco, abdominal aorto-iliac calcium, coronary artery calcium

As marijuana use is increasingly legalized and prescribed for medical conditions, the public health community's interest in informing the public about potential health effects of marijuana use has also grown.(1) In 2013, annual prevalence of marijuana use was 7.5 to 9.4 percent in the U.S. population.(2, 3) In 2014, up to 17% of the US population smoked tobacco. Marijuana and tobacco smoke share many constituents.(4) Whereas the negative health effects of tobacco smoke are widely known,(5) per recent National Academy of Science report there is little information about possible adverse health consequences of marijuana, including the harm prolonged and heavy use might cause to the cardiovascular system.(6, 7)

Computed tomography can detect atherosclerosis before clinical symptoms appear which makes it a measure of subclinical atherosclerosis. Abdominal aorto-iliac calcium (AAC) and coronary artery calcium (CAC) scores are better predictors of incident coronary heart disease and cardiovascular disease (CVD) than standard risk factors and other well-known biomarkers.(8, 9) Tobacco smoke is a known cause of atherosclerosis and tobacco use is also a strong predictor of AAC and CAC.(10) However, we do not know yet if marijuana smoke also causes atherosclerosis and we found only one previous prospective cohort study which has assessed the association between cumulative marijuana use and CAC.(11) Cumulative smoking and marijuana use were significantly associated with multiple

plaque measures, but with negligible effect sizes for marijuana.(11) To the best of our knowledge, no previous study has tested the association between cumulative marijuana use and AAC.

On the basis of case reports, some have voiced concern that increased marijuana use may spur a new CVD epidemic.(12) Cohort studies can better isolate the possible association of marijuana with CVD. A large cohort of 49 321 conscripted Swedish men aged 18 to 20 at the time of inclusion and followed over 40 years found a trend towards increased risk of stroke in heavy marijuana smokers after multivariate adjustment.(13) However, investigators only collected data on marijuana use at the time of inclusion which might have led to imprecise estimates of the true marijuana exposure and explain the null findings. In contrast, marijuana and tobacco smoking and other covariates associated with marijuana use and atherosclerosis have been measured repeatedly in CARDIA participants for 25 years.

We tested the association between cumulative marijuana use and ACC and CAC measures, and accounted for cumulative tobacco exposure, and other measures associated with atherosclerosis and marijuana and tobacco use.

METHODS

Study Design and Sample

We used data collected over 25 years in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a population-based epidemiological study of 5,115 adults aged 18 to 30 years at baseline.(14) Participants were recruited in 1985 and 1986 by randomly selecting telephone numbers from designated census tracts in Birmingham, AL; Chicago, IL; Minneapolis, MN; and, by random selection from the membership list of a health care plan in Oakland, CA. The sampling scheme was designed to achieve equal proportions at each of the four sites by race (self-identified “black, not Hispanic” and “white, not Hispanic”), sex, education (up to a high school degree, education beyond high school), and age (18-24 years, 25-30 years). All subjects gave informed consent before entering the study, and at

each follow-up examination. The study was approved by institutional review boards for each site.

Marijuana and Tobacco Smoking Exposure

Current marijuana use was assessed at each in-person CARDIA examination (at baseline and at 2, 5, 7,10,15, 20, and 25 years of follow-up) by the following survey question: “During the last 30 days, on how many days did you use marijuana?” Direct self-reported lifetime exposure was assessed by the question: “About how many times in your lifetime have you used marijuana?” We used current and lifetime use to compute marijuana-years: one year of exposure was equivalent to 365 days of marijuana use.(15) We assumed that current use at each survey (i.e., the number of days the participant used marijuana in the month before each survey) reflected the average number of days of use in the months between surveys. We estimated cumulative lifetime use by adding up the total number of days the participant used marijuana over the entire follow-up period. We adjusted our estimate upwards whenever participants self-reported higher lifetime use than we computed.(15, 16)

Cigarette smoking behavior was evaluated at each in-person CARDIA examination, and at yearly phone follow-up between CARDIA examinations.(15) At baseline, participants were asked the total number of years they had smoked, the age at which they started smoking regularly (“How old were you when you started smoking cigarettes regularly?”) and, if appropriate, years since cessation (“How many years ago did you stop?”). We used these data to estimate cumulative lifetime exposure to cigarettes in terms of pack-years: one pack-year of exposure was equivalent to 7300 cigarettes (1 year×365 days/y×1 pack/d×20 cigarettes/pack).(15, 16) Occasional smoking was not queried in CARDIA.

Outcome Measures: Coronary artery calcium and abdominal aortic calcium

The primary outcome variables were presence of CAC and AAC (total calcification score > 0 Agatston units) measured at year 25.(17) We used computed tomography (CT) to assess subclinical coronary atherosclerosis (presence of any CAC or AAC at year 25 [2010–2011]).(18) To measure CAC, we obtained contiguous 2.5-3-mm-thick transverse images

from the root of the aorta to the apex of the heart.(19) To measure AAC, we obtained 1-1.25-mm-thick transverse images 15-cm proximal to the superior end plate of the sacrum.(19) We measured calcium in the wall of the distal abdominal aorta in a 60-mm segment centered at the aortic bifurcation. Images collected at each center were then transmitted electronically to the CARDIA Reading Center.(18) Total CAC and AAC scores were calculated by image analysts blinded to participant characteristics; they used a modified Agatston method, with select over-reading by a physician expert in cardiovascular imaging.

Other Covariates

We estimated cumulative years of exposure to passive smoking. We defined one year of exposure to passive smoking as the total number of hours exposed to passive smoking over 24h, for 365 days (eMethods in Online Data Supplements).(20) We estimated lifetime alcohol consumption in "drink-years." We defined one drink-year as the amount of alcohol consumed by a person in one year of drinking one drink/day (eMethods).(15) We defined acute heavy exposure to alcohol (bingeing) as five or more drinks consumed on one occasion, and we estimated total lifetime bingeing episodes. We estimated total number of lifetime exposures to cocaine (including crack, powder, free base), amphetamines (speed, uppers, methamphetamines), and heroin (eMethods).(15, 21)

The highest educational grade attained for each participant was the measure of education. We measured physical activity with the CARDIA Physical Activity History questionnaire, which asks how much time per week the participant spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.(22) We measured self-reported depressive symptoms every five years, starting at Year 5, on the Center for Epidemiologic Studies Depression scale (CES-D).(23) Our cardiovascular risk factor measurements included blood pressure, blood cholesterol (total-, LDL-, HDL-cholesterol and triglycerides), fasting glucose and body mass index (BMI) which were collected at each CARDIA exam (eMethods). We calculated cumulative exposures to cardiovascular risk factors, physical activity and depression symptoms (eMethods).(15, 24)

Statistical analyses

We used descriptive statistics to compare participants with different levels of marijuana exposure at Year 25. We then described unadjusted associations between lifetime marijuana use and presence or absence of AAC or CAC. In our primary analysis, we used multinomial regression models to assess independent associations between years of exposure to marijuana. We compared three categories of subclinical atherosclerosis: 1) no AAC and no CAC; 2) any AAC and no CAC; and, 3) CAC, regardless of AAC. We found history of exposure to tobacco smoking significantly interacted with the association between cumulative exposure to marijuana and AAC, in both unadjusted and multivariate adjusted multinomial regression models (*P*=<0.1) (eTable 2). We therefore stratified all results and analyses by history of exposure to tobacco smoking. First, we estimated unadjusted models. Then, we estimated multivariate adjusted models, controlling for covariates to achieve balanced sampling in CARDIA (age, race, sex, study site and years of education) and for covariates potentially associated with both marijuana and subclinical atherosclerosis (cigarette smoking, alcohol, cocaine, amphetamines and heroin, exposure to passive smoking, cardiovascular risk factors, physical activity, BMI, depression symptoms, and diabetes). We used restricted cubic splines with three knots at the quartiles of their distributions to flexibly model marijuana-years of exposure, pack-years, and years of exposure to passive smoking. We used inverse probability of censoring weights (IPCWs) to minimize potential bias by informative censoring (eMethods).(25, 26) We tested whether sex and race interacted, and evaluated the sensitivity of the results to alternate strategies for modeling subclinical atherosclerosis using multivariate adjusted logistic regression models to contrast (a) participants with and without AAC, (b) those with and without CAC and, (c) those with AAC and CAC and those with no AAC and no CAC. We tested sensitivity of the results to alternate modeling techniques: 1) A multivariate adjusted model that included an interaction term between history of exposure to tobacco smoking and cumulative exposure to marijuana; 2) a multivariate adjusted model that compared participants according to history of exposure to marijuana and tobacco (a) no history of exposure to tobacco or marijuana, b) history of exposure to tobacco and not to marijuana, c) no history of exposure

to tobacco and history of exposure to marijuana, and d) history of exposure to both tobacco and marijuana*;* 3) a set of multivariate regressions that enabled us to model AAC and CAC as continuous measures (eMethods). We further evaluated the proportion of participants who might have been mixing tobacco with marijuana to smoke marijuana (mulling) at baseline by measuring blood cotinine levels, and then we tested the sensitivity of the results to excluding participants with cotinine levels suggestive of tobacco exposure and no self-reported use of tobacco at baseline (eMethods).(27-29) Tests of statistical significance were 2-tailed; alpha level was 0.05. All analyses were conducted with STATA 14.2 (StataCorp LP, College Station, TX).

RESULTS

Of the 3,498 participants assessed at the Year 25 visit, 3,197 (91%) had data entries for AAC or CAC, and 3,117 (89%) had complete AAC and CAC data (eFigure 1 in Online Data Supplements). Attrition was more common among men, Blacks, heavy marijuana users, tobacco smokers, and cocaine users in multivariate adjusted analyses (eResults). In unadjusted analyses, attrition was associated with age, race, gender, education, and smoking (eTable1 in Online Data Supplements). Most participants (n=2627,84%) reported having used marijuana before or during the 25 years of follow-up, but most had relatively few cumulative years of exposure (Table 1). Among marijuana users, a minority (n=156, 6%) reported having used marijuana every day in the month before a CARDIA exam. Among those, the median number of joints smoked per day at the Year 10 exam was 2 (interquartile range: 1 to 3). In contrast, 1,536 (49%) reported ever smoking tobacco daily. Cumulative exposure to tobacco was high; 42% of ever smokers reported smoking 10 pack-years. Total years of marijuana exposure was strongly associated with other participant characteristics, including race and sex, education, study site, other substance use, physical activity, BMI, HDL-cholesterol and triglycerides, and depressive symptoms (Table 1). Among those who *never* smoked tobacco, 73% (N=1,155) were *ever* marijuana users; among *ever* tobacco smokers, 96% (N=1,472) were *ever* marijuana users (Table 1).

Among those who *never* smoked tobacco, cumulative marijuana-years were associated with CAC in unadjusted analyses, but not with AAC (Table 2). Multivariate adjusted multinomial models that categorized presence and absence of AAC and CAC into three categories: AAC=0 & CAC=0, AAC>0 & CAC=0, CAC>0, regardless of AAC revealed lifetime exposure to marijuana was not associated AAC and CAC (Table 3 and Figure 1, Panels A and B). Only 26 participants were exposed to marijuana for 10 marijuana-years (equivalent to using marijuana every day for 10 years, or four a week for 14 years): their OR for CAC regardless of AAC was 1.63 (95% confidence internals (CI):0.81-3.29;Table 3).

Among those who *ever* smoked tobacco daily, cumulative marijuana-years were associated with AAC and CAC in unadjusted analyses (Table 2). In multivariate logistic

regression models, at one year of exposure to marijuana, the OR for AAC and no CAC was 1.36 (95%CI:1.07-1.71) and CAC regardless of AAC was 1.29 (95%CI:0.98-1.69;Table 3,Figure 1,Panels C and D). In multivariate logistic regression models that compared AAC with no AAC, cumulative marijuana use was associated with AAC only among *ever* tobacco smokers (Table 4). Sensitivity analyses demonstrated no evidence of significant interactions by race or sex ($p>0.10$ for all tests). Results were similar when we included an interaction term between history of exposure to tobacco smoking and cumulative exposure to marijuana, instead of stratifying results by history of exposure to tobacco (eTable 2). We found no association between AAC or CAC and history of exposure to marijuana among those with no history of exposure to tobacco, and found significant associations among those with history of exposure to marijuana and tobacco (eTable2 in Online Data Supplements). Modeling AAC or CAC as continuous outcomes resulted in OR similar to those returned by the main models (eTable 4).

Tobacco smoking was strongly associated with both AAC and CAC in unadjusted and multivariate adjusted analyses. The OR at 10 pack-years of tobacco was 5.86 (95%CI:3.64-9.45) for AAC and no CAC and 6.61 (95%CI:3.92-11.14) for CAC regardless of AAC (Table 3,Figure 1,Panels E and F).

Among participants who reported no tobacco smoking at baseline, 4% had cotinine levels suggestive of exposure to tobacco among those reporting no marijuana use within the last 30 days and 11% among those reporting marijuana use within the last 30 days (eTable). Results were virtually unchanged when we excluded participants with cotinine levels suggestive of exposure to tobacco exposure and no self-reported use of tobacco (eTable 6).

DISCUSSION

In this community-based cohort of young adults, followed for 25 years, we found little or no significant association between cumulative marijuana use and either AAC or CAC. Among those who had never used tobacco, marijuana use was not significantly associated with AAC or CAC, but we identified a trend towards increased risk of AAC and CAC among those whose cumulative exposure to marijuana was high (5 marijuana-years, equivalent to smoking marijuana daily for 5 years). Among ever tobacco smokers, using marijuana daily for five years nearly doubled the odds of AAC and CAC. As expected, cumulative tobacco smoking exposure was strongly associated with both AAC and CAC. The vast majority of participants had been exposed to marijuana in their lifetime, but few had more than 365 days of cumulative exposure, and few used it daily. In contrast, half of participants reported they had smoked tobacco daily, and most had smoked 20 cigarettes a day for at least 5 years.

Previous analyses of the participants in CARDIA study showed no association between marijuana use and cardiovascular events, or mortality overall.(30, 31) One possibility for such lack of association was hypothesized to be due to the mean age of participants (around 50), which is younger than the age at which most CVD occurs. Therefore, our current study is able to provide timely insight on any relationship of marijuana with subclinical atherosclerosis.

We found only one previous study which had tested the association between CAC and cumulative marijuana use, and found no previous studies having tested the association with AAC.(11) The 1005 participants in the Multicenter AIDS Cohort Study (MACS) participants (621 HIV+ and 384 HIV-) underwent non-contrast CT scanning to measure CAC when they were aged 54, on average. Participants were queried on self-reported use of substances at semiannual visits over 10 years. Cumulative pack-years of smoking and marijuana were significantly associated with multiple plaque measures, but with negligible effect sizes for marijuana.(11) Our null finding among never tobacco users could be explained by the opposing effects marijuana may have on atherosclerosis.(32) Besides the combustion constituents of marijuana smoke,(4) the main component of marijuana smoke is

tetrahydrocannabinol (THC), which activates the CB_2 and CB_1 receptors of the endocannabinoid system. Activating the CB_2 receptor might protect marijuana smokers from developing atherosclerosis, since this regulates inflammatory cells and been shown to reduce atherosclerosis in mice.(33) Activating the CB_1 receptor, on the other hand, might increase atherosclerosis(34) since *inhibiting* CB_1 might protect against atherosclerosis.(35, 36) The trend toward increasing atherosclerosis that we found among those whose cumulative exposure to marijuana was high might be caused by combustion constituents of marijuana smoke other than THC.(4, 37) In the CARDIA cohort, cumulative marijuana exposure was low among those who had used the drug—much lower than cumulative tobacco exposure among ever tobacco users. Our null findings might thus also be explained by the low intensity of marijuana use in our cohort. It remains possible that smoking marijuana every day over many years could cause as much harm as smoking tobacco cigarettes.

Acute exposure to marijuana might have negative effects on heart disease since it can increase heart rate and could trigger arrhythmias by activating the CB_1 receptor and precipitating an MI.(38, 39) The acute effect of marijuana might explain one study's finding of a surge in MI just after marijuana use.(39) The absence of evidence of an increase in subclinical atherosclerosis in our study and the absence of significant association with CVD events in previous analyses in CARDIA,(30) suggest that even if marijuana can trigger an acute MI, it is does not increase the atherosclerotic process that leads to MI.

Our study also has some limitations. We found cumulative marijuana use was significantly associated with ACC among ever tobacco smokers, but we cannot rule out residual confounding by tobacco smoking. Tobacco smokers who use marijuana might also be more likely to smoke a mix of tobacco and marijuana ('mulling').(28, 29) When we explored the associations between blood cotinine levels based on self-reported exposure to tobacco and marijuana smoking, we found 7% of participants not reporting smoking tobacco might have been mulling at baseline (11% in those not reporting currently using marijuana vs. 4% in those reporting currently using marijuana). Blood cotinine was only measured at

baseline, so we cannot estimate the prevalence of mulling over follow-up or estimate the amount of mulling among participants who reported tobacco use. Our marijuana exposure measurements are derived from self-reports, which are less reliable than blood or urine tests. Marijuana use was measured infrequently; examinations can be up to five years apart, and this reduced the precision of the estimates. CARDIA also did not ask how old participants were when they began using marijuana, so we only could estimate exposure before the start of the study by looking at participants' own estimates of the number of times they had been exposed to marijuana.

Our study was strengthened by extensive adjustment for a wide range of potential confounders, and by particularly detailed data on primary and secondary tobacco exposure and other licit and illicit drug exposures. We also used advanced methods to adjust for cardiovascular risk factors in our models of cumulative exposures. The proportion of participants followed up to 25 years was high, and our statistical methods took into account potential informative censoring.(25, 26) Though it was difficult to fully adjust for tobacco exposure, because many participants said they had not smoked tobacco in their lifetime, we could test the association in those who only used marijuana. We had data on AAC and CAC scores, which are among the strongest predictors of incident coronary heart disease.(8, 40, 41)

Our results mostly apply to occasional, recreational users of marijuana whose exposure is low overall. Larger studies with longer follow-up are needed to confirm absence or presence of association between marijuana and subclinical atherosclerosis and CVD events. It would be useful to explore the trend towards increased odds of AAC and CAC with high cumulative use of only marijuana, based on data from large cohorts, rigorous measures, and extensive follow-up. If the trend is real, it may have implications for medical marijuana users, since they often use marijuana daily over many years. These studies are urgently needed to inform medical marijuana patients and prescribers about possible CVD risks associated with smoking medical marijuana.

Marijuana and tobacco use were both common, but the intensity of lifetime tobacco smoking was consistently much higher than marijuana. Cumulative marijuana use was not associated with measures of atherosclerosis among middle-aged adults never exposed to tobacco, but we saw a trend towards increased risk of atherosclerosis among those with very high exposure to marijuana. These results should be interpreted carefully since few participants had such high exposure. Among those who had used tobacco, we found a small but significant association between marijuana use and AAC, even after we extensively adjusted for tobacco smoke exposure, but this may have been due to residual confounding. Our study confirms the strong and consistent association between tobacco use and both AAC and CAC; the broader public health implications of high prevalence of tobacco use among marijuana users is alarming.

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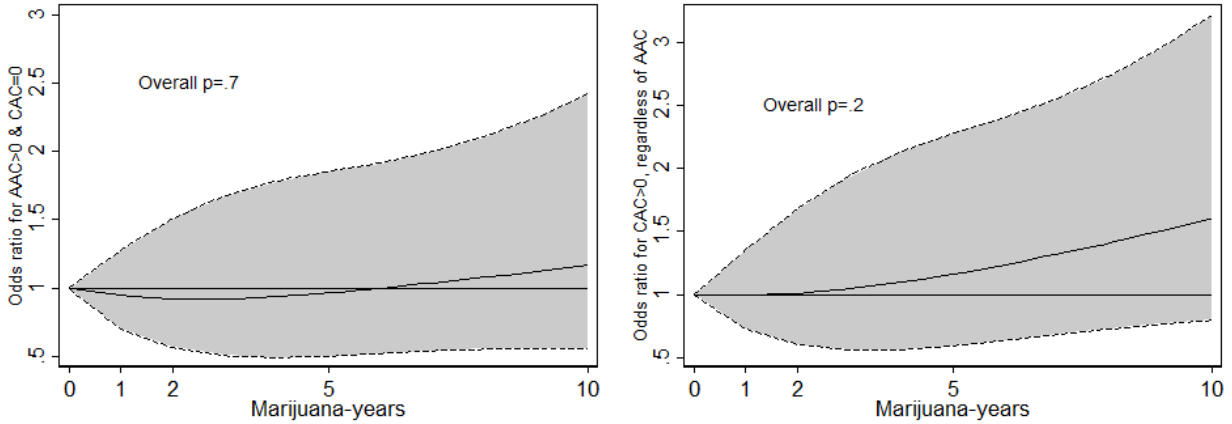
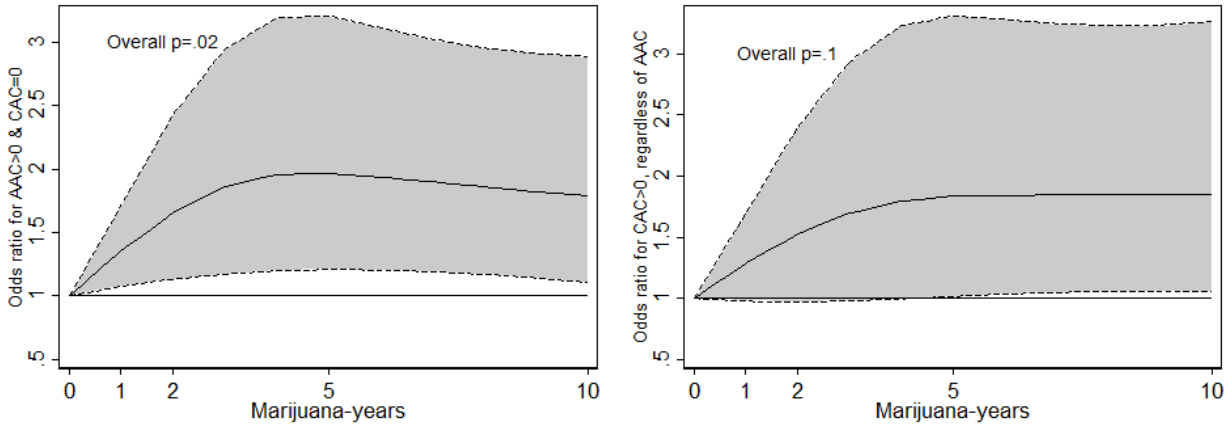
Panel A and B. Marijuana-years among *never* tobacco smokers (N=1581).



Panel C and D. Marijuana-years among *ever* tobacco smokers (N=1536).



Panel E and F. Tobacco pack-years among *ever* smokers (N=1536).

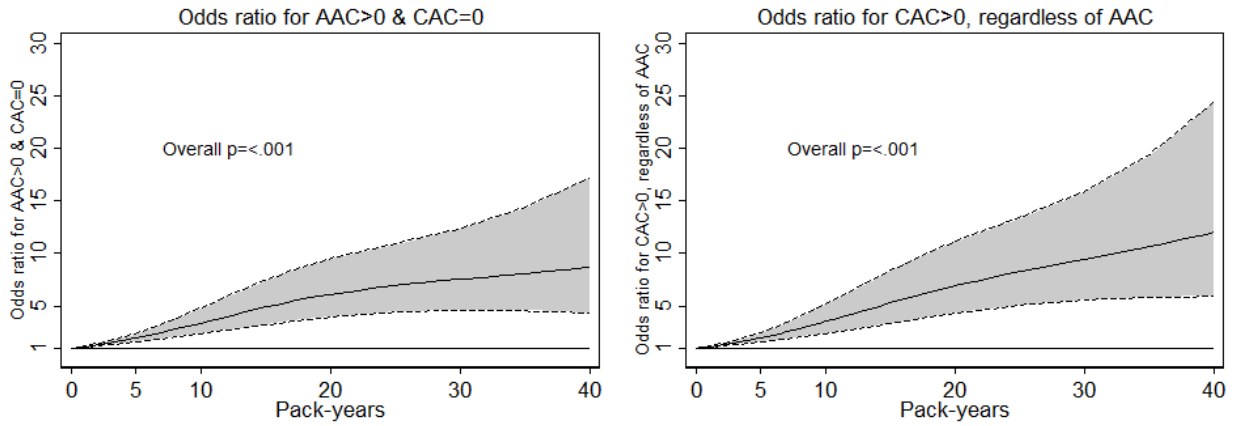


Figure 1: Associations between cumulative exposures to marijuana and tobacco and AAC and CAC. Multivariate adjusted multinomial logistic regression models showing an absence of association between higher exposure to marijuana and greater odds of AAC > 0 & CAC = 0 (Panel A) and CAC > 0, regardless of ACC (Panel B) compared to AAC=0 and CAC=0 among *never* tobacco smokers. Among *ever* tobacco smokers, models show a significant association between higher exposure to marijuana for AAC > 0 & CAC = 0 (Panel C), but not for CAC > 0, regardless of ACC (Panel D) compared to AAC=0 and CAC=0. For tobacco pack-years of exposure, models show a significant and dose-response association for both AAC > 0 & CAC = 0 (Panel E), and CAC > 0, regardless of ACC (Panel F) compared to AAC=0 and CAC=0. Scale of the axis presenting the Odds ratio multiplied by 10 to present the association with tobacco pack-years. Multivariate models adjusted for covariates potentially associated with marijuana, tobacco and subclinical atherosclerosis: age, race, sex, study site, years of education, exposure to illicit and licit substances (alcohol, cocaine, amphetamines and heroin use, exposure to passive smoking), cardiovascular risk factors, physical activity, BMI, depression symptoms, and diabetes (Methods). Analyses were weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring (eMethods).

Table 1. Characteristics of 3117 CARDIA Participants with CAC and AAC measures at the Year 25 Exam, by Never/Ever Tobacco Use and Cumulative Marijuana Use.

	Never Tobacco Smoker N=1581 (51%)			Ever Tobacco Smoker N=1536 (49%)		
	No marijuana use	>0 to <1 marijuana-years	>1 marijuana-years	No marijuana use	>0 to <1 marijuana-years	>1 marijuana-years
N, (row %)‡	426 (14)	947 (30)	208 (7)	64 (2)	787 (25)	685 (22)
Demographics						
- Age, mean (SD), y	49.6 (3.9)	50.1 (3.6)	50.9 (3.4)	50.3 (3.8)	50.5 (3.6)	50.0 (3.6)
- Race-sex, N (col. %)§						
Black women	155 (36)	274 (29)	31 (15)	27 (42)	256 (33)	150 (22)
Black men	65 (15)	130 (14)	57 (27)	15 (23)	112 (14)	207 (30)
White women	102 (24)	300 (32)	41 (20)	14 (22)	278 (35)	134 (20)
White men	104 (24)	243 (26)	79 (38)	8 (13)	141 (18)	194 (28)
- Years of education, median (Q1, Q3), y	16 (14, 18)	16 (15, 18)	16 (14, 17)	16 (12, 18)	15 (14, 17)	14 (14, 16)
- Study center, N (col. %)						
Birmingham, AL	185 (43)	192 (20)	24 (12)	35 (55)	183 (23)	111 (16)
Chicago, IL	111 (26)	211 (22)	33 (16)	11 (17)	189 (24)	152 (22)
Minneapolis, MI	81 (19)	209 (22)	65 (31)	13 (20)	222 (28)	235 (34)
Oakland, CA	49 (12)	335 (35)	86 (41)	5 (8)	193 (25)	187 (27)
Substance use exposure						
Current marijuana use, N (col. %)‖						
- No current use	426 (100)	932 (98)	139 (67)	64 (100)	762 (97)	425 (62)
- 1-10 days per month	-	15 (2)	34 (17)	-	25 (3)	138 (20)
- 11 to 29 days per month	-	0 (0)	26 (13)	-	0 (0)	71 (10)
- 30 days per month (everyday)	-	0 (0)	9 (4)	-	0 (0)	51 (7)

Cigarette smoking, N (col. %)						
- Current smoker	-	-	-	17 (26)	222 (28)	314 (46)
- Former smoker	-	-	-	47 (73)	565 (72)	371 (54)
- Age started smoking cigarettes, median (Q1, Q3)	-	-	-	22 (17, 32)	17 (15, 21)	17 (15, 19)
Cumulative use						
- Pack-years over lifetime, median (Q1, Q3)[¶]	-	-	-	2 (0.3, 11)	6 (1, 14)	10 (3, 21)
Passive smoke exposure						
- Years of passive smoke exposure, median (Q1, Q3)[#]	0.5 (0.2,1.2)	0.6 (0.2,1.3)	0.8 (0.4,1.8)	1.1 (0.5,2.6)	1.7 (0.6,3.5)	2.6 (1.2,5.1)
Alcohol use, N (col. %)[**]						
Cumulative use						
- Drink-years among ever drinkers, median (Q1, Q3)[††]	8 (3, 16)	13 (6, 24)	22 (11, 37)	8 (3, 27)	19 (9, 32)	29 (15, 57)
- Binge drinking days, cumulative use, N (col %)[‡‡]						
- Never reported bingeing	350 (82)	551 (59)	60 (29)	44 (69)	310 (40)	130 (19)
- ≤ 250 days	51 (12)	251 (26)	64 (30)	11 (17)	259 (33)	199 (29)
- > 250 days	25 (6)	145 (15)	84 (40)	9 (14)	218 (28)	356 (52)
Cumulative illicit drug use[§§]						
- Cocaine, crack, speed or metamphetamine, N (col. %)						
- Never reported using	417 (98)	602 (64)	31 (15)	60 (94)	274 (35)	57 (8)
- 1 to 25 days	7 (2)	219 (23)	45 (22)	2 (3)	232 (30)	96 (14)
- > 25 to 250 days	1 (<1)	100 (10)	77 (37)	1 (2)	167 (21)	223 (33)
- > 250 days	1 (<1)	26 (3)	55 (26)	1 (2)	114 (14)	309 (45)
- Heroin, N (col. %)						

- Never reported using	414 (97)	897 (95)	157 (75)	63 (98)	672 (85)	467 (68)
- 1- 25 days	10 (2)	41 (4)	31 (15)	0 (0)	74 (9)	89 (13)
- ≥ 25 days	2 (<1)	9 (1)	20 (10)	1 (2)	41 (5)	129 (19)
Physical activity						
- Physical activity score, median (Q1, Q3)[IIII]	234 (82, 427)	269 (143, 490)	393 (215, 601)	166 (49, 315)	268 (121, 471)	298 (144, 487)
Anthropomorphic variables						
- BMI, mean (SD)[¶¶]	31.9 (7.3)	30.0 (7.3)	30.0 (5.9)	29.5 (7.1)	30.3 (7.4)	29.7 (6.6)
Cardiovascular risk factors						
- Systolic blood pressure, mean (SD), in mmHg	120 (16)	118 (15)	120 (16)	120 (18)	120 (17)	122 (16)
- Diastolic blood pressure, mean (SD), in mmHg	75 (11)	74 (11)	75 (12)	75 (12)	75 (11)	77 (11)
- LDL-cholesterol, mean (SD), in mg/dl	114 (33)	113 (31)	115 (34)	112 (36)	112 (35)	110 (32)
- HDL-cholesterol, mean (SD), in mg/dl	55 (15)	59 (18)	55 (16)	57 (21)	60 (19)	57 (19)
- Triglycerides, mean (SD), in mg/dl	108 (73)	108 (76)	120 (79)	111 (64)	115 (97)	126 (106)
- Diabetes, N (%)	58 (14)	112 (12)	23 (11)	11 (17)	132 (17)	89 (13)
Psychological variables						
- Depression symptoms, current CES-D ≥16/60, N (%)[##]	59 (14)	111 (12)	32 (15)	10 (16)	134 (17)	131 (19)

Abbreviations: BMI: body mass index; CARDIA, Coronary Artery Risk Development in Young Adults study; CES-D: Center for Epidemiologic Studies Depression scale; Col. %: column percent; LDL: low density lipoprotein (LDL); HDL: high density lipoprotein; N: number of participants; Q1, Q3: 1st and 3rd quartile (percentile 25 and 75); SD, standard deviation

[*] Cumulative lifetime exposure to marijuana joints in terms of marijuana-years, with 1 marijuana-year of exposure equivalent to 365 days used marijuana (1 year × 365 days/y) (see Methods and eMethods in Online Data Supplements).(16, 42)

[‡] Row percent are presented for binary variables and column percents for variables with more than one category.

[§] By design, the CARDIA study sampled self-identified white men, white women, black men and black women in roughly equal numbers for participation in the study.(43)

[‖] Categories based on the answer to the question: “During the last 30 days, on how many days did you use marijuana?”

[¶] Cumulative lifetime exposure to cigarettes in terms of pack-years, with 1 pack-year of exposure equivalent to 7300 cigarettes (1 year × 365 days/y × 1 pack/d × 20 cigarettes/pack)(Methods).(16)

[#] Cumulative lifetime exposure to second hand cigarette smoke in terms of years of second hand smoking exposure with 1 year of exposure equivalent to 8700 hours of exposure (1 year × 365 days/y × 24 hours per day)(Methods).(20)

[††] Drink-years among those reporting ever drinking alcohol. A drink-year was defined as the total amount of ethanol consumed by a person who had one alcoholic drink per day for 1 year (1 drink-year = 17.24 ml of ethanol/drink × 1 drink/day × 365 days/year = 6,292.6 ml of ethanol).

[‡‡] Binge-drinking days defined as 5 or more drinks per episode (eMethods in Online Data Supplements). If bingeing were to be constant over 25 years in one individual, 250 binge drinking days would correspond to 10 episodes of bingeing per year over 25 years.

[§§] The number of days on the illicit drug listed over the study duration was computed using current exposure (current use defined as any use within the last 30 days) at each visit and replaced by lifetime exposure when the latter was higher. Cocaine included other forms of cocaine such as crack, powder, free base; amphetamines included speed, uppers and methamphetamines (Methods and eMethods in Online Data Supplements).

[‖‖] Physical activity measured with the CARDIA Physical Activity History questionnaire, which queries the amount of time per week spent in 13 categories of leisure, occupational, and household physical activities over the past 12 months.(22)

[¶¶] Calculated as weight in kilograms divided by height in meters squared.

[##] Depression symptoms was measured every five years starting at the Year 5 visit by using the Center for Epidemiologic Studies Depression scale (CES-D).(23) A score of ≥16 used as the cut-off value for both sexes as an indication of the clinically significant depressive symptoms.(44)

Table 2. Association between life-time exposure to marijuana and measures of subclinical atherosclerosis among never and ever tobacco users, CARDIA, year 25

	Total	Never Tobacco smoker				p-value†	Ever Tobacco smoker				p-value†
		Total	No marijuana use	>0 to <1 marijuana-years	>1 marijuana-years		Total	No marijuana use	>0 to <1 marijuana-years	>1 marijuana-years	
N, (col %)	3117 (100)	1581(100)	426 (100)	947 (100)	208 (100)		1536 (100)	64 (100)	787 (100)	685 (100)	
3 categories, N, (col %)											
- AAC = 0 & CAC = 0	1246 (40)	770 (49)	211 (50)	478 (50)	81 (39)		476 (31)	26 (41)	279 (35)	171 (25)	
- AAC > 0 & CAC = 0	982 (32)	432 (27)	123 (29)	252 (27)	57 (27)	.005	550 (36)	15 (23)	283 (36)	252 (37)	<.001
- CAC > 0, regardless of AAC	889 (29)	379 (24)	92 (22)	217 (23)	70 (34)		510 (33)	23 (36)	225 (29)	262 (38)	
2 categories (binary outcome)											
- AAC > 0, N, (% compared to AAC=0)	1663 (53)	679 (43)	187 (44)	394 (41)	98 (47)	.3	984 (64)	32 (50)	473 (60)	479 (70)	<.001
- CAC > 0, N, (% compared to CAC=0)	889 (29)	379 (24)	92 (22)	217 (23)	70 (34)	.002	510 (33)	23 (36)	225 (29)	262 (38)	<.001
- AAC > 0 or CAC > 0, N, (% compared to AAC=0 & CAC=0)	1871 (60)	811 (51)	215 (50)	469 (50)	127 (61)	.01	1060 (69)	38 (59)	508 (65)	514 (75)	<.001

† p-values from χ^2 test across categories.

Table 3. Association between lifetime exposure to marijuana and measures of subclinical atherosclerosis and among never/ever tobacco users, CARDIA, year 25*

	Never tobacco smokers		*Ever* tobacco smokers	
	Unadjusted models (N=1581)‡	Multivariate adjusted models (N=1562)§	Unadjusted models (N=1536)‡	Multivariate adjusted models (N=1502)§
Cumulative exposure in marijuana-years				
(a) AAC =0 & CAC =0	Ref.	Ref.	Ref.	Ref.
(b) AAC >0 & CAC =0				
- At 0.5 marijuana-years	1.00 (0.88 to 1.13)	0.97 (0.82 to 1.14)	1.19 (1.09 to 1.32)	1.18 (1.04 to 1.34)
- At 1 marijuana-years	1.00 (0.80 to 1.26)	0.95 (0.70 to 1.28)	1.39 (1.17 to 1.66)	1.36 (1.07 to 1.71)
- At 5 marijuana-years	1.09 (0.68 to 1.74)	0.98 (0.51 to 1.88)	2.11 (1.47 to 3.03)	1.97 (1.21 to 3.21)
- At 10 marijuana-years	1.25 (0.72 to 2.17)	1.20 (0.58 to 2.48)	1.92 (1.35 to 2.75)	1.78 (1.10 to 2.89)
p-value‖	0.7	0.6	<0.001	0.02
(c) CAC >0 regardless of AAC				
- At 0.5 marijuana-years	1.18 (1.05 to 1.33)	0.99 (0.84 to 1.18)	1.22 (1.10 to 1.34)	1.15 (0.99 to 1.33)
- At 1 marijuana-years	1.37 (1.10 to 1.69)	1.00 (0.73 to 1.36)	1.44 (1.20 to 1.72)	1.29 (0.98 to 1.69)
- At 5 marijuana-years	2.33 (1.51 to 3.63)	1.17 (0.60 to 2.30)	2.42 (1.68 to 3.51)	1.83 (1.02 to 3.31)
- At 10 marijuana-years	2.85 (1.74 to 4.66)	1.63 (0.81 to 3.29)	2.51 (1.76 to 3.58)	1.85 (1.05 to 3.26)
p-value‖	<0.001	0.2	<0.001	0.1
Cumulative exposure in tobacco pack-years				
(b) AAC >0 & CAC =0				
- At 5 tobacco pack-years	-	-	1.85 (1.54 to 2.21)	1.90 (1.53 to 2.36)
- At 10 tobacco pack-years	-	-	5.70 (3.96 to 8.20)	5.86 (3.64 to 9.45)
- At 40 tobacco pack-years	-	-	9.63 (5.15 to 17.99)	8.80 (4.25 to 18.21)
p-value‖			<0.001	<0.001
(c) CAC >0 regardless of AAC				
- At 5 tobacco pack-years	-	-	1.83 (1.52 to 2.21)	1.93 (1.52 to 2.44)
- At 10 tobacco pack-years	-	-	6.68 (4.58 to 9.73)	6.61 (3.92 to 11.14)

- At 40 tobacco pack-years	-	-	18.19 (9.8 to 33.64)	12.54 (5.92 to 26.55)
p-value [ll]			<0.001	<0.001

Abbreviations: IPCW: Inverse probability of censoring weighting; Ref.: Reference

[*] Cumulative exposure to marijuana expressed in 'marijuana-years', with 1 marijuana-year of exposure equivalent to 365 days of marijuana use.(see Methods).

[‡] Multinomial logistic regression models with three categories of subclinical atherosclerosis: 1) no AAC and no CAC; 2) any AAC and no CAC; and, 3) CAC, regardless of AAC as the outcome and cumulative exposure to marijuana or tobacco smoking modeled as restricted cubic splines, stratified by history of exposure to tobacco smoking (Methods).

[§] Model described in [‡] additionally adjusted for age, race, sex, study site, years of education, cumulative and current exposure to licit and illicit substances such as cigarette smoking, alcohol, cocaine, amphetamines and heroin, exposure to passive smoking, cardiovascular risk factors, physical activity, BMI, depression symptoms, and diabetes (Methods). Analyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring (eMethods).

[ll] p-values obtained by Wald-test across the entire variable contrasting the reference value to the AAC/CAC category.

Table 4. Estimated ORs from multivariate adjusted model at five marijuana-years of exposure

	Never tobacco smokers		*Ever* tobacco smokers	
	OR (95% CI) at 5 marijuana-years	P-value	OR (95% CI) at 5 marijuana-years	P-value
Multinomial model (3 categories)				
- AAC =0 & CAC =0	Ref.		Ref.	
- AAC >0 & CAC =0	0.98 (0.51 to 1.88)	.9	1.97 (1.21 to 3.21)	.007
- CAC >0 regardless of AAC	1.17 (0.60 to 2.30)	.6	1.83 (1.02 to 3.31)	.04
Logistic regressions (2 categories)				
- AAC =0 regardless of CAC	Ref.		Ref.	
- AAC >0 regardless of CAC	0.89 (0.53 to 1.52)	.7	1.84 (1.18 to 2.08)	.007
- CAC =0 regardless of AAC	Ref.		Ref.	
- CAC >0 regardless of AAC	1.20 (0.65 to 1.26)	.6	1.18 (0.72 to 1.92)	.5
- AAC =0 & CAC =0	Ref.		Ref.	
- AAC >0 or CAC >0	1.07 (0.63 to 1.85)	.8	1.91 (1.20 to 3.05)	.006

Note: Only participants with both AAC and CAC measures at year 25 included. Multivariate models stratified by history of tobacco smoking, adjusted for covariates potentially associated with marijuana and subclinical atherosclerosis: age, race, sex, study site, years of education, exposure to illicit and licit substances (cigarette smoking, alcohol, cocaine, amphetamines and heroin use, exposure to passive smoking), cardiovascular risk factors, physical activity, BMI, depression symptoms, and diabetes (Methods). Analyses weighted by the inverse probability of censoring (IPCW) to address potential bias by informative censoring (eMethods).